II. REMARKS

Formal Matters

Claims 1-65, 67, and 82-83 have been cancelled without prejudice or disclaimer. Applicants reserve the right to file one or more continuing applications on the canceled subject matter. Claim 66 has been amended to recite "predicting the likelihood of response of the patient to treatment with cetuximab by comparing the normalized level of the LAMC2 transcript to gene expression data obtained from reference samples derived from patients with colon cancer . . . ." Support for the amendment can be found, for example, in Example 2 of the specification. Claim 66 has also been amended to recite "wherein an increased normalized level of LAMC2 RNA transcript correlates with a decreased likelihood of response to treatment with cetuximab." Support for the amendment can also be found, for example, in Example 2 of the specification, and at paragraph [0096] and Table 3. Thus, the amendments are fully supported by the specification and do not add new matter.

Upon entry of these amendments, claims 66 and 68-81 are under consideration.

Rejection Under 35 U.S.C. §112, First Paragraph

Claims 66 and 68-83 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement for the following reasons.

First, the Office points out that claim 66 recites "wherein an increased normalized level of LAMC2 RNA transcript correlates with resistance of the colon cancer to treatment with cetuximab"; and alleges that the claims do not define what the increase is in comparison to. Office Action at p. 4. Further, the Office alleges that the claims do not indicate how the increased level of LAMC2 RNA correlates with resistance to treatment with cetuximab, i.e. "does increased LAMC2 RNA mean there is an increased or decreased likelihood of response to treatment with cetuximab?" *Id.*

Applicants respectfully disagree. Nonetheless, without acquiescing to the rejection, and solely in an effort to further prosecution, Applicants have amended claim 66 to recite "predicting the likelihood of response of the patient to treatment with cetuximab by comparing the normalized level of the LAMC2 transcript to gene expression data obtained from reference samples derived from patients with colon cancer, wherein an increased normalized level of LAMC2 RNA transcript correlates with a decreased likelihood of response to treatment with cetuximab." Thus, Applicants believe that this rejection is rendered moot.

Second, the Office points out that claim 82 further comprises determining the normalized level of one or more additional predictive RNA transcripts recited in the claim. *Id.* The Office alleges that several of the genes did not have statistically significant p values and therefore alleges that the specification does not teach a reliable association between these genes and response to treatment with an EGFR inhibitor. Office Action at p. 6.

Applicants respectfully disagree. Nonetheless, without acquiescing to the rejection, and solely in an effort to further prosecution, Applicants have canceled claims 82 and 83 without prejudice or disclaimer. Thus, Applicants respectfully request withdrawal of this rejection.

Finally, the Office alleges that it is highly unpredictable if one can predict the likelihood that a human colon cancer patient will exhibit a clinically beneficial response to treatment with cetuximab. Office Action at p. 7. The Office argues that since none of the patients that were given cetuximab responded to treatment, one would not know what the expression level of LAMC2 would be in a patient that responded to treatment with cetuximab. Office Action at p. 8. Furthermore, the Office alleges that the finding that the three patients who responded to EMD 72000 had lower levels of LAMC2 RNA compared to patients who did not respond or had progressive disease does not necessarily mean that patients who respond to cetuximab will also have lower levels of LAMC2 RNA compared to patients

who did not respond or had progressive disease. *Id.* In this respect, the Office cites to Solmi (BMC Cancer 8:227, 2008), a post-filing date paper, as evidence that treatment with different EGFR inhibitors results in different gene expression patterns and thus, findings with one drug cannot be extrapolated to another drug. *Id.*

Applicants respectfully traverse the rejection.

The test of enablement is whether one reasonably skilled in the art could make and use the invention from the disclosure in the application coupled with information known in the art without undue experimentation. MPEP §2164.01. The Office has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. MPEP § 2164.04. If the Office has weighed all the evidence and established a reasonable basis to question the enablement for the claimed invention, the burden falls on applicant to present persuasive arguments, supported by suitable proofs where necessary, that one skilled in the art would be able to make and use the claimed invention using the application as a guide. MPEP § 2164.05. Applicants may provide evidence after the filing date that demonstrates that the claimed invention works. *Id.* The evidence provided by applicant need not be conclusive but merely convincing to one skilled in the art. *Id.* (emphasis original).

As explained in prior responses, Applicants assert that the claimed invention is fully enabled by the specification. For example, the specification teaches that increased expression of LAMC2 correlated with resistance of colon cancer to EGFR inhibitor treatment. *See* p. 29, paragraph [0102]. Table 3 indicates that LAMC2 correlated with a "negative" response, meaning that greater expression of LAMC2 decreased the likelihood of response to treatment with EGFR inhibitor. *See also* paragraph [0096], p. 28. While the data in Table 3 are based on three responders treated with the EGFR inhibitor EMD 72000, the specification teaches that "the findings of the present invention are equally applicable to other EGFR inhibitors, including without limitation, anti-EGFR antibodies . . . ." Paragraph [0085],

p. 26. The specification discloses cetuximab, a monoclonal antibody that blocks the EGFR and EGFR-depending cell growth, as another example of an EGFR inhibitor. Paragraph [0081] at p. 26.

As additional evidence that the findings in the instant application are indeed equally applicable to cetuximab, Applicants submit U.S. Patent App. Pub. No. 2009/0298701 ("the '701 publication"), published December 3, 2009. The '701 publication reports the analysis of normalized levels of gene products from tumors obtained from patients that had undergone cetuximab treatment for colon cancer, commensurate in scope with the instant claims. *See* '701 publication, paragraphs [0253] – [0283], p. 21-23. Example 2 of the '701 publication reports genes whose normalized expression correlated with Overall Response Rate (ORR) in 226 colon cancer patients treated with cetuximab. *See* '701 publication, paragraph [0298], p. 23. LAMC2 is listed in Table 1B (p. 24) as being negatively correlated with ORR with a p value of 0.0204 based on examination of the 226 patients (N=226). Similarly, Example 3 of the '701 publication reports genes whose normalized expression correlated with Disease Control (DC) in 226 colon cancer patients treated with cetuximab. *See* '701 publication, paragraph [0299], p. 24. LAMC2 is again listed in Table 2B as being negatively correlated with DC with a p value of 0.0006 based on examination of the 226 patients (N=226).

The Office contends that it is unpredictable if the claimed method works as such further experimentation would be required. Office Action at p. 10. The Office suggests that such experimentation may involve treating a large number of colon cancer patients with cetuximab, assaying the expression levels of LAMC2, and then monitoring the patients to determine disease outcome. *Id.* The Office alleges that such random, trial by error experimentation is considered to be undue. *Id.* However, as explained above, the claimed method can be used to predict the likelihood that a human colon cancer patient will exhibit a clinically beneficial patient response to treatment with an EGFR inhibitor such as cetuximab, as first disclosed in the instant application and further shown in the '701

publication. Thus, the claimed invention is not unpredictable and does not require undue experimentation.

Accordingly, Applicants believe that claims 66 and 68-81 are fully enabled under 35 U.S.C. §112, first paragraph. The Office is thus respectfully requested to withdraw the rejection.

III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Office finds that a telephone conference would expedite the prosecution of this application, the Office is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number GHDX-005.

Respectfully submitted,

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Date: August 31, 2010

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